IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAIHO PHARMACEUTICAL CO., LTD. and TAIHO ONCOLOGY, INC., Plaintiffs, v. EUGIA PHARMA SPECIALITIES LTD., AUROBINDO PHARMA LTD., and AUROBINDO PHARMA U.S.A., INC., Defendants.	)	C.A. No. 19-2309-CFC
TAIHO PHARMACEUTICAL CO., LTD. and TAIHO ONCOLOGY, INC., Plaintiffs, v. ACCORD HEALTHCARE INC., Defendant.	)	C.A. No. 19-2321-CFC
TAIHO PHARMACEUTICAL CO., LTD. and TAIHO ONCOLOGY, INC., Plaintiffs, v. MSN LABORATORIES PRIVATE LTD. and MSN PHARMACEUTICALS, INC., Defendants.	)	C.A. No. 19-2342-CFC-JLH

TAIHO PHARMACEUTICAL CO., LTD. and TAIHO ONCOLOGY, INC.,	)	
Plaintiffs,	)	C.A. No. 19-2368-CFC-JLH
v.	)	
NATCO PHARMA LTD. and NATCO PHARMA, INC.	)	
Defendants.	)	

DEFENDANTS' POST-TRIAL REPLY BRIEF

RICHARDS LAYTON & FINGER, P.A.
Kelly E. Farnan
Tyler E. Cragg
One Rodney Square
920 N. King Street
Wilmington, DE 19801
(302) 651-7700

Attorneys for Defendants Natco Pharma Ltd. and Natco Pharma Inc.

MORRIS JAMES
Kenneth Laurence Dorsney
Cortlan S. Hitch
500 Delaware Avenue
Suite 1500
Wilmington, DE 19899-2306
(302) 888- 6855

Attorneys for Defendants Eugia Pharma Specialities Ltd., Aurobindo Pharma Ltd., and Aurobindo Pharma U.S.A., Inc.

SMITH, KATZENSTEIN, & JENKINS LLP
Neal C. Belgam
Daniel A. Taylor
1000 West Street, Suite 1501
Wilmington, DE 19801
302-652-8400

Attorneys for Defendants Accord Healthcare Inc., MSN Laboratories Private Ltd., and MSN Pharmaceuticals Inc.

Dated: May 11, 2023

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES & RULES

I. INTRODUCTION

Defendants respectfully submit that the testimony at trial established by clear and convincing evidence that claim 13 of the '284 patent is invalid as obvious under 35 U.S.C. § 103. By January of 2005, the administration of TAS-102 to colorectal cancer patients in two divided portions per day on an established weekends off dosage schedule is simply not the kind of activity that warrants further patent protection. *Graham v. John Deere Co.*, 383 U.S. 1, 14 (1966). Claim 13 also is invalid for lack of written description under 35 U.S.C. § 112. Nothing in Taiho's Answering Post-Trial Brief supports a basis to conclude otherwise.

To the contrary, Taiho's Brief contains multiple arguments not supported by the trial record. The first paragraph of Taiho's introduction illustrates this point. Claim 13 of the '284 patent (the only claim at issue) is not "a groundbreaking cancer treatment using trifluorothymidine (FTD)" as Taiho argues. Claim 13 simply recites the administration of a known composition (TAS-102), on a known dosing schedule, in two divided portions per day. No witness at trial testified that, by January of 2005, artisans had all but abandoned TAS-102 "for its lack of clinical utility." Pls.' Br. at 1.

The trial record establishes that Taiho had published results from three prior art Phase I clinical trials from 2000-2002, each reporting on efforts to

improve the clinical utility of TAS-102. Defs.' Br. at 17-20. The prior art also includes Emura II (2004), a pre-clinical study reporting that dividing the daily TAS-102 dose would enhance incorporation of the anticancer component of the composition (FTD) into the DNA of cancer cells. *Id.* at 5-6. It is irrelevant that these investigators worked for Taiho; their publications are undisputed prior art to the '284 patent. No artisans abandoned TAS-102 "for its lack of clinical utility," and none of this prior art "taught away from the claimed method," as Taiho now asserts.

II. MANY OF TAIHO'S POST-TRIAL ARGUMENTS DO NOT APPEAR IN THE TRIAL RECORD

As discussed below, Taiho's brief reflects a deliberate effort to revise the trial record through its post-trial brief with citations to exhibits that are largely not supported by any witness testimony. This post-trial revisionist practice is fundamentally improper and has long been rejected in the District of Delaware. *Alza Corp. v. Andrx Pharms., LLC,* 607 F. Supp. 2d 614, 622 (D. Del. 2009) (striking portions of proposed post-trial findings advancing written description defense that was not presented in pre-trial briefing or at trial), *aff'd on other grounds*, 603 F.3d 935 (Fed. Cir. 2010); *Mobil Oil Corp. v. Amoco Chemicals Corp.,* 779 F. Supp. 1429, 1441 n.5 (D. Del. 1991) (inventorship defense not presented at trial was waived), *aff'd,* 980 F.2d 742 (Fed. Cir. 1992).

This practice is grounded in the recognition that the presentation of arguments in post-trial briefing that were not the subject of any trial testimony effectively prevents defendants from being able to present competing testimony **during trial**. *Allergan Inc. v. Barr Labs*, 808 F. Supp. 2d 715, 735 (D. Del. 2011) (Judge Robinson concluding the defendants "have switched horses by combining pieces of testimony . . . into new obviousness theories" post-trial and refusing to entertain such arguments post-trial); *aff'd*, 501 Fed. Appx. 965 (Fed. Cir. 2013).

To prevent such unfairness, a district court need not consider post-trial arguments that differ remarkably from the testimony and arguments presented at trial. *Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc.*, 282 F. Supp. 3d 793 n.4 (D. Del. Oct. 13, 2017) (declining to consider arguments raised for the first time in post-trial briefing because party "failed to make these arguments at trial.").

Taiho had every opportunity to raise all the issues it desired at trial. Taiho's effort to re-frame its arguments now is too late and should be summarily rejected. *E.I. Du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 656 F. Supp 1343, 1378-79 (D. Del. 1987) (court refusing to consider arguments raised for the first time in post-trial briefing).

A. No Trial Testimony Supports Taiho's Argument that Claim 13 Involves a "deeply unpredictable area in a deeply unpredictable art"

One example of a new horse Taiho hopes to ride post-trial is its argument that the hypothetical investigator[1] would understand "the administration of FTD, specifically [to be] a deeply unpredictable area in a deeply unpredictable art." Pls.' Br. at 4. Taiho provides no citation to any witness who so testified at trial. Moreover, Taiho did not contend at trial that, by January of 2005, the administration of TAS-102 to colorectal cancer patients in divided doses was a "deeply unpredictable" endeavor for the hypothetical investigator. In fact, no witness testified at trial that the administration of TAS-102 (much less FTD alone) was unpredictable as of January of 2005.

At best, Mr. Mita testified that "human functions are unpredictable and mysterious beyond one's imagination." Tr. at 268:14-16 (Mita). This testimony is unclear and lacks scientific vigor. In contrast, Dr. Ratain testified that

---

[1] Defendants used the term "hypothetical investigator" in place of "POSA" or "person of ordinary skill in the art" merely to simplify the nomenclature. Tr. at 93:20-94:19. There was no dispute at trial that this hypothetical person "would be able to interpret the results of preclinical and early clinical trials involving chemotherapy drug combinations," and would work on a team with scientists "who work on the chemistry associated with the development of solid oral dosage forms." Tr. at 94:6-9. Defendants used the term "hypothetical investigator" at trial without objection from Taiho. *Id.* Its use in Defendants' brief was in no way an effort to apply a different "POSA standard," as Taiho now suggests. Pls.' Br. at 3.

dividing the dose of TAS-102 twice a day was common sense. Tr. at 160:14-25. Dr. Goldberg also testified that the iterative process of adjusting the daily dose was "a standard approach to drug development, yes." Tr. at 399:7-17 (Goldberg). Thus, Taiho's new "deeply unpredictable" rhetoric is just attorney argument presented in its post-trial briefing, unsupported by the trial record.

B. No Trial Testimony Supports Taiho's Argument that FTD's Mechanism of Action Was Not Well Understood by January of 2005

Another stark example of a new horse that Taiho hopes to ride post-trial begins on page 3 of Taiho's Brief, where Emura II (DTX 11) is cited in a sequence of four sentences. Relying on Emura II, Taiho lists predicate facts alleged to support the conclusion that "[c]hoosing whether and how to safely and effectively divide the daily dose of TAS-102 and the schedule on which it should be administered was not 'simple' nor well understood at the time the application that led to the '284 patent was filed." Pls.' Br. at 3. Taiho's new argument is that "FTD operates differently" from other cancer agents, because it is dependent upon "the amount of time that it was in physical contact with cancer cells," and "the more time, the better." *Id.* at 5 (referring to Section III.C.1). Taiho suggests that this allegedly unique mechanism of action would have taught "a *higher* number of doses" per day and would have "affirmatively taught away from a two-dose divided regimen." Pls.' Br. at 5. However, no

witness testified on these issues at this trial and Taiho cites only to Emura II (DTX 11).

This same argument also can be found later in Taiho's Brief (at pages 14-16), where Taiho cites to Emura II (DTX 11) and concludes that "TAS-102 can therefore produce its intended anticancer effect *only if* the patient receives the appropriate total daily dose, *and* that total daily dose is divided into the appropriate number of portions, *and* that daily dose is administered on the proper schedule." *Id.* at 14 (emphasis in original). Taiho employs this argument to suggest that the dosing regimen of claim 13 is complex, and such complexity is an additional element of claim 13 not disclosed in the prior art. *Id.* at 14-15.

Again, Taiho cites no trial testimony to support this interpretation of Emura II or claim 13. In fact, no witness at trial provided testimony interpreting Emura II or claim 13 in this manner. This is post-trial attorney argument alone, and should be disregarded by the Court.

C. No Trial Testimony Supports Taiho's New "DCR" Theory, Calculated from Hoff, Dwivedy, and Thomas

Another egregious example of a new horse that Taiho is hoping to ride post-trial relates to a new argument concerning a "disease control rate" ("DCR"). The DCR, according to a footnote in Taiho's Brief, is "an indication of a drug's efficacy." Pls.' Br. at 25, n.6. According to Taiho's Brief, the DCR values are calculated based on the number of patients in each study that were

reported to have demonstrated "stable disease," as compared to those not demonstrating "stable disease." Pls.' Br. at 25 n.6 (citing to Exhibit Q in Mr. Mita's declaration). No witness testified about these DCR calculations at trial, based on Hoff, Dwivedy, and Thomas. Taiho employs these post-trial calculations in an effort to argue that Hoff, Dwivedy, and Thomas would have "taught away" from the method of claim 13. Pls.' Br. at 24-27. Taiho also asserts (with no citation to supporting trial testimony) that Dwivedy reported the lowest disease control rate, and that the hypothetical investigator "would not have retreated back to the dosing schedule that produced the lowest DCR." Pls.' Br. at 25-26. The same argument also can be found at page 17, where Taiho asserts that (as compared to the Hoff and Thomas) "the Dwivedy regimen proved less effective." Pls.' Br. at 17. There is no trial testimony by any witness supporting any of these DCR arguments.

Respectfully, the Court should reject Taiho's attempts to present new arguments via post-trial briefing. It is simply not fair to "change horses" on so many different fronts when the trial record is closed, and the Defendants are prevented from introducing responsive trial testimony. *Allergan Inc.* 808 F. Supp. 2d at 735.

III. THE TRIAL RECORD ESTABLISHES OBVIOUSNESS BY CLEAR AND CONVINCING EVIDENCE

A. Taiho Conceded at Trial that the Only Difference Between Claim 13 and the Prior Art is Twice-a-day Dosing

As explained above, Taiho now suggests the mechanism of action associated with FTD establishes that aspects of claim 13 are absent from the prior art beyond simply dosing TAS-102 in two divided portions per day. Pls.' Br. at 14-16 (Section III. C.1.). Taiho waived this argument, as it was not made at trial.[2]

Assuming the Court nonetheless entertains this new argument, the trial record unequivocally establishes that Taiho conceded (multiple times) that "all the dosage parameters," except for the administration of 2 divided portions of the claimed composition per day, "are in the prior art." Tr. at 546:11-17. Taiho also conceded at trial that dosing FTD "[o]ne, four, six, and eight" times per day was in the prior art. Tr. at 547:3-5. Taiho additionally conceded (twice) at trial that there is nothing in the prior art that says twice daily administration of TAS-102 would fail. Tr. at 546:8-10; 547:6-8. Pages 14 through the first half of page 16 of Taiho's Brief is a blatant attempt to backtrack from this central concession.

---

[2] Taiho is also presenting a straw man argument. Defendants have never argued that *all* claim elements are explicitly in the prior art, and such a finding is not required to establish obviousness. 35 U.S.C. § 103.

B. "Obvious to Try" Is Not Defendants' Sole Basis of Obviousness

Defendants' Opening Post-Trial Brief articulates the evidence in the trial record that establishes ample reason for the hypothetical investigator: 1) to have been motivated to combine the teachings of Dwivedy with Emura II; 2) to arrive at the claimed method; 3) with a reasonable expectation of success. Defs.' Br. at 26-34. Taiho did not seriously challenge this evidence at trial.

As explained below, there was no evidence at trial pointing the hypothetical investigator as of January 2005 in an "opposite direction" when it came to dividing the daily dose of TAS-102 administered to patients. Pls.' Br. at 1, 5, 6, 20, 21. Still, Taiho declares Defendants' case was "relegated" to an "obvious to try" theory and proceeds to attack only that rubric. This is simply not true. Defendants' case is not solely dependent upon an "obvious to try" theory.

However, even if it were true that Defendants' case was solely based on an "obvious to try" theory, Defendants still met their burden. The clear and convincing evidence of obviousness that Defendants summarized in their opening brief establishes that dividing the TAS-102 dose into either two or three portions a day was clearly "a finite number of identified predictable solutions" that were available to the hypothetical investigator by January of 2005. The administration of TAS-102 in two divided daily doses certainly was not a "new

technology or general approach that seemed to be a promising field of experimentation." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). And Emura II does not give only "general guidance" on the way to administer TAS-102 to colorectal cancer patients. 853 F.2d at 903.

The fact remains, as Taiho repeatedly admitted at trial, that the only element of claim 13 not explicitly disclosed in the prior art is the administration of two, rather than three, divided daily doses of TAS-102. Tr. at 546:11-17. For this reason, the facts of this case simply do not line up with *In re O'Farrell*, or *Grunenthal v. Alkem*. Pls.' Br. at 20. Plaintiffs' reliance on *Grunenthal* is also misplaced because Emura II specifically directs the hypothetical investigator that dividing the daily dose will enhance the activity of the composition. Tr. at 155:4-8 (Ratain). Further, common sense would lead the artisan to simply divide the dose into two portions per day. Tr. at 163:21-164:11 (Ratain testifying one would be motivated to modify the schedule "until you see an objective response," and the hypothetical investigator "would use divided dosing, either two or three times per day.").

C. Taiho's Various "Teaching Away" Arguments Are Not Supported by the Record and Are Not Legally Tenable

Taiho presents three different "teaching away" arguments in its brief, each of which is new, not supported by the trial record, or simply wrong. Each argument is addressed below, but Defendants respectfully refer the Court to its

Opening Post-Trial Brief, at pages 27-29. As set forth therein, no evidence suggests that the prior art discouraged the hypothetical investigator from proceeding to administer TAS-102 with twice-daily dosing. The prior art blazed a path for the investigator to follow—it did not discourage an investigator from twice-daily dosing on the Dwivedy schedule. Dr. Ratain testified that basic common sense would have guided the hypothetical investigator to administer TAS-102 in two divided portions per day (Tr. at 160:17-21), and there is no credible testimony in the trial record supporting a contrary finding.[3]

Assuming Plaintiffs' 'teaching away' argument is considered, Emura II does not criticize twice daily dosing of TAS-102 or suggest that it should not be tried. A reference teaches away only "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken" in the claim. *Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009). In contrast, a reference does not teach away when it "merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into" the

---

[3] Dr. Ratain's testimony that twice-daily dosing would be common sense also rebuts Plaintiffs' argument that Defendants have used the incorrect "POSA" standard. Pls.' Br. at 12.

claimed invention. *Id.*; *see also Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013).

(1) The "Full Scope of Prior Art" Does Not Teach Away from Claim 13

Taiho's first "teaching away" argument proclaims, "the full scope of prior art" would have taught away from the method of claim 13. Taiho argues "the Dwivedy regimen proved less effective," and that the Dwivedy schedule is only one of among several other dosing schedules available in the prior art. Pls.' Br. at 17. As set forth below, Taiho's assertion that the Dwivedy schedule proved less effective relies upon a post-trial "DCR" calculation, which (if not disregarded) is speculative and unsupported by the trial record.

Taiho's "mosaic-like" argument is another new post-trial horse. Defendants have never contended that the hypothetical investigator must "selectively pick and choose from a number of dosing schedules used in clinical trials of other chemotherapy drugs (e.g. UFT and S-1)". Pls.' Br. at 17. Further, at no point in the trial did Taiho argue, nor did any witness testify, that the task before the hypothetical investigator would have been complicated by various other studies, involving other chemotherapy drug combinations. Proof of Taiho's post-trial change of theory is evinced by the testimony of Dr. Goldberg, who testified that a hypothetical investigator "would have looked at all of the

data available," and agreed on direct that there was a reason a POSA would combine Dwivedy and Emura II. Tr. at 349:16-24.

If considered, this argument is unavailing. Dr. Goldberg conceded that the investigators who published Dwivedy chose the weekends off schedule because they had successfully completed another clinical trial, using the same schedule with a different chemotherapy drug combination. Tr. at 423:14-424:1. The weekends off schedule in the prior study (DTX 247 using UFT plus leucovorin) had allowed the investigators to administer a higher daily dose of the oral chemotherapy drug than had been used in a prior study. Tr. at 421:17-422:21.

Specifically, Dr. Goldberg agreed that the Dwivedy investigators decided to use the weekends off schedule with TAS-102 **because of** the prior study. Tr. at 423:14-19. He also agreed that this process of learning from other studies with different drugs is "part of the iterative process for persons of ordinary skill in the art" in the relevant time frame. Tr. at 423:20-424:4. This refutes the "teaching away" theme Taiho now proffers. Defendants' case does not rely upon "only some portions of" contemporary studies using other chemotherapy drugs, and Taiho's contention otherwise is simply not supported by the record.

(2) The Prior Art Did Not Teach Away from Using Two Divided Portions Per Day of FTD

Taiho's second "teaching away" argument rests upon Taiho's post-trial theory that the half-life, mechanism of action, and toxicity of FTD "all taught away from the claimed invention," and asserts that "two divided doses was in the opposite direction and contrary to the teachings of the prior art." Pls.' Br. at 20-21. This is another one of Taiho's new post-trial arguments that should be disregarded. Again, Taiho conceded at trial that there is nothing in the prior art that says twice-daily dosing fails. Tr. at 546:8-10; 547:6-8.

Setting aside Taiho's concession, large sections of Taiho's post-trial argument rely only upon citations to Emura II, with no supporting witness testimony. Pls.' Br. at 21-24. No witness testified that the hypothetical investigator would have understood that Emura II "would have taught a POSA to continue moving toward three or more (smaller, more frequent) divided dose portions per day, rather than to move backward to two (larger, less frequent) divided dose portions per day." *Id.* at 23. This inference is attorney argument alone, unsupported by trial testimony.

If considered, Emura II does not criticize twice daily dosing of TAS-102 or suggest that it should not be tried. In fact, Dr. Ratain explained that from a commercial and patient perspective, "two would be the desirable number of doses, given that one was believed not to be enough doses per day." Tr. at

161:20-25. He also testified that twice daily dosing would be obvious based on "just basic common sense, that if you want to divide the dose, two is the smallest number of doses per day." Tr. at 160:14-21.

Dr. Goldberg, when asked to explain "why Emura [II] perhaps suggested that three times was an optimal dosing schedule," only testified that Emura II "suggested that exposure to significant drug levels over ten hours would be ideal. And that's why, I believe, he used three doses, three hours apart." Tr. at 348:10-21. Dr. Goldberg did not testify that the hypothetical investigator would have administered TAS-102 to patients in "three or more (smaller, more frequent) divided dose portions per day, rather than to move backward to two (larger, less frequent) divided dose portions per day" as Taiho now contends. This is another new post-trial horse that should also be disregarded. *Allergan Inc.* 808 F. Supp. 2d at 735.

Furthermore, Emura II does not criticize twice daily dosing of TAS-102 or suggest that it should not be tried. Thus, it cannot be said to teach away from twice-daily dosing. *See Depuy Spine*, 567 F.3d at 1327; *Galderma Labs.*, 737 F.3d at 738. Dr. Ratain testified that Emura II experimented with giving TAS-102 to mice either in one or in three divided portions per day. Tr. at 153:13-154:4. Dr. Ratain explained that Emura II taught the hypothetical investigator that dividing the dose results in "enhancement of the antitumor effects of TAS-

102 without any additional side effects, [and that] it is concluded that multiple daily dosing may result in better clinical benefits for TAS-102 when compared with single daily dosing." Tr. at 154:17-155:25. He also opined that Emura II tells "our hypothetical investigator that, you know, you need to use more than one dose per day in your clinical trials." Tr. at 155:1-8. (Ratain); DTX 11 at 1. Dr. Ratain concluded that Emura II would tell the hypothetical investigator "three is better than one, but [Emura II] certainly doesn't tell you three is optimal." Tr. at 158:24-159:8. Dr. Goldberg never substantively rebutted this testimony.

Dr. Ratain's testimony is credible and confirms that Emura II did not "discredit, or otherwise discourage" the use of two divided portions of the TAS-102 dose each day. In sum, the prior art does not teach away from twice-daily dosing of TAS-102. Neither Emura II nor any of the other prior art of record actively discourages, disparages, or even suggests that twice-daily dosing would not work or should not be tried by clinical investigators. Accordingly, Plaintiffs' second "teaching away" argument is not credible, nor legally tenable.

(3) The Prior Art Did Not Teach Away from Using the Dwivedy Weekends Off Dosing Schedule

Taiho's third "teaching away" argument focuses on the three prior Phase I abstracts (Hoff, Dwivedy, and Thomas). Pls.' Br. at 24-26. Taiho recites the chronological sequence of these three abstracts as "the iterative process

involving TAS-102," and relies upon its new DCR calculations from each abstract to assert that Defendants "willfully ignore the dosing schedule taught by Thomas." *Id.* at 25. As stated above, Taiho waived any argument based upon its new DCR calculations by not presenting any calculations of the DCR values at trial. There was no testimony by any witness concerning DCR values that the hypothetical investigator might have calculated from the data reported in Hoff, Dwivedy, and Thomas.

Assuming the Court considers this third argument, the record evidence does not support Taiho's assertion that the hypothetical investigator would have started with Thomas, as Taiho now suggests. To the contrary, Dr. Goldberg, when summarizing what a hypothetical investigator would understand once Thomas published, explained that each of the three studies gave a dose "in different amounts because the schedules were different," and that all three studies "resulted in success in one way and failure in another." Tr. at 346:4-11. His testimony was **not** that the investigator would be discouraged by the results of any single study but rather would have concluded that "more preliminary work was required before a successful strategy could be identified." Tr. at 346:2-17.

Moreover, the Thomas study was done for a different purpose[4] than Hoff and Dwivedy. *See* Tr. at 18:1-8 (Defendants' Opening Statement). Thomas reports the study "was designed to determine the maximum tolerated dose (MTD) for a *more dose-intense regimen*." PTX-0538 (emphasis added). Accordingly, the patients in Thomas began with a 100 mg/m^2/day dose and were escalated to 140 mg/m^2/day. *Id.* It would make no sense for the hypothetical investigator to focus only on Thomas alone, to the exclusion of the teachings of Hoff and Dwivedy, keeping in mind the iterative drug development process.

Finally, Taiho's new theory that the DCR values calculated from Hoff, Dwivedy, and Thomas would have discouraged the hypothetical investigator from arriving at the claimed administration schedule (Pls.' Br. at 25) is pure speculation. According to Taiho's Brief, the DCR values are calculated based on the number of patients in each study that were reported to have demonstrated "stable disease," as compared to those not demonstrating "stable disease." Pls.' Br. at 25 n.6 (citing to Exhibit Q to Mr. Mita's declaration). However, Dr.

---

[4] Defendants recognize there is no trial testimony on this point. However, it is possible that the higher DCR calculated from Thomas is due to the higher doses that were administered to the patients in the study. Had these calculated DCR values been raised at trial, both parties could have asked each expert more questions about this topic, and whether the DCR values calculated from Hoff, Dwivedy, and Thomas would have meaningfully deterred the hypothetical investigator from exploring further dosing schedules for TAS-102.

Ratain explained that "stable disease" is not an interpretable metric in a Phase I study, explaining "I have seen so much stable disease in Phase I trials of completely ineffective agents that it doesn't mean anything to me when I see it." Tr. at 123: 3-11. He also explained that even a finding of a "prolonged stable disease" is "hard to interpret in a Phase I trial." Tr. at 189:20-22; *see also* Tr. at 219:20-25 and 223:9-16 (explaining patients can demonstrate stable disease with a placebo, and stable disease is not necessarily a drug effect).

Further, Dr. Birkhofer (Taiho's medical director) testified by deposition that "stable disease" is an "uninterpretable sign," as follows:

> **Q.** And a patient in a study like this demonstrating a stable disease state for more than three months, that's – that's a good sign, right?
> **A.** Actually, it's an uninterpretable sign. You know, I think in most Phase I studies, I think people are looking for actual evidence of tumor shrinkage, not stable disease.

Tr. at 252:11-17. Assuming the Court considers Taiho's new "DCR" theory as a basis for supporting a new "teaching away" argument, the available trial testimony establishes that DCR values calculated from "stable disease" observations in Phase I clinical trials are "uninterpretable" and, therefore speculative.

D. Secondary Indicia of Nonobviousness Do Not Overcome Defendants' Strong *Prima Facie* Case of Obviousness

Defendants respectfully submit its Opening Post-Trial Brief overall adequately addresses the secondary considerations proffered by Taiho at trial.

The following reply points are intended only to respond to Taiho's Brief on specific points not directly addressed in Defendants' Opening Brief.

(1) The Claimed Dosing Regimen Did Not Lead to Unexpected Results

Taiho's Brief improperly suggests the Court should be "extremely reluctant" to reject Mr. Mita's declaration alleging "surprising and unexpected results encompassed by claim 13" submitted to the USPTO because that declaration convinced the USPTO to issue the claim. Pls.' Br. at 11 (*Broussard v. Go-Devil Mfg. Co.*) and 35-36 (*MiMedx Grp., Inc. v. Tissue Transplant Tech., Ltd.*). Taiho apparently believes this Court has no business upsetting this allegedly "technical finding" by the Patent Office, asserting that some heightened deference must be afforded to the Patent Office by an Article III District Court. Pls.' Br. at 35. This is not the law.

The Federal Circuit has explained that district courts appropriately reach an independent conclusion on the validity of a challenged patent, even when a patent has survived a reexamination and the court is presented with the same references that the USPTO considered. *See Exmark Mfg. Co. Inc. v. Briggs & Stratton Power Prods. Grp., LLC*, 879 F.3d 1332, 1341 (Fed. Cir. 2018). A district court "is never bound by an examiner's finding in an ex parte patent application proceeding." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007). Likewise, an examiner's findings during reissue proceedings are not

binding. *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1555 (Fed. Cir. 1985). Rather, the "deference [owed] to the decisions of the USPTO takes the form of the presumption of validity under 35 U.S.C. § 282." *Pfizer*, 480 F.3d at 1359 (citations omitted).

Plaintiffs' reliance on *Broussard v. Go-Devil Mfg. Co.* is particularly flawed for several reasons. *Broussard* involved resolution of a summary judgment motion, and the Louisiana court determined it would be improper "to *completely disregard* the USPTO's findings *at this stage*." No. 3:08-CV-00124-BAJ, 2014 WL 46632, at *3 (M.D. La. Jan. 6, 2014) (emphasis added). In a later decision on the merits, the same court ultimately found the disputed patent claim was obvious "despite the PTO's determination to the contrary[,]" noting "[t]he PTO's opinion regarding the validity of [the patent at issue] loses much of its persuasive force in light of the evidence presented at trial." 29 F. Supp. 3d, 753, 782 (M.D. La. July 9, 2014). Just like here, the evidence at trial in *Broussard* was that the USPTO heavily relied on a declaration that "fell far short of providing a complete assessment of [the patent as issue's] validity[.]" *Id.* at 782-83.

Finally, on appeal, the Federal Circuit clarified that although the district court "must consider the reexamination as evidence, it is not bound by the PTO's decision." *Gator Tail, LLC v. Mud Buddy LLC*, 618 Fed.Appx. 992, 998

(Fed. Cir. 2015). The Federal Circuit affirmed the Louisiana court's determination that "the trial testimony [was] a more complete picture of the evidence, and [] that the PTO decision on reexamination deserved less weight." And, the patent was held invalid. *Id.* The *Broussard* case therefore does not support Taiho's position.

Accordingly, the presumption of validity "is just that—a *presumption*—which can be overcome by the patent challenger who meets its high burden of proving the factual elements of invalidity by clear and convincing evidence." *Exmark*, 879 F.3d at 1341 (emphasis in original). In short, a district court has an obligation to reach an independent conclusion based on the evidence presented at trial, regardless of the conclusions reached by the USPTO.

In light of the trial record before this Court, Mr. Mita's testimony (including the declaration he submitted to the Patent Office) is not persuasive and does not establish unexpected results. As Dr. Ratain explained, the presentation of data in the Mita declaration compared "apples and oranges," and "[y]ou just can't compare those two studies," because "[i]t makes no scientific or medical sense." Tr. at 221:11- 21. It is well within this Court's discretion to reject Mr. Mita's self-serving assertions of unexpected results. *Bayer AG v. Housey Pharms., Inc.* 386 F.Supp.2d 578, 581-582 (D. Del. 2005) (finding inventor testimony lacked credibility), *aff'd*, 189 Fed. Appx. 969 (Fed. Cir.

2006). This is especially true when Taiho reported to the FDA that the same studies demonstrated "no antitumor effect." Tr. at 175:12-21; Tr. at 178:13-17; 178:23-179:6 (Ratain).

(2) Mr. Mita's Alleged Invention Story Was Not Credible

Plaintiffs' alleged invention story that "***Mr. Mita proposed moving backward***. . ." lacks credibility because it was based on uncorroborated hearsay.[5] Pls.' Br. at 29 (emphasis in original). No colleague of Mr. Mita, or member of Taiho's "TAS-102 team," corroborated Mr. Mita's testimony that his colleagues "could not believe it – believe the possibility" that two divided doses per day might work. Tr. at 268:19-269:4.

This Court would be within its discretion to disregard Mr. Mita's testimony entirely. Courts in this district have consistently discounted inventor's testimony regarding what a POSA would think and whether results of their own studies were surprising. *See Purdue Pharma L.P. v. Accord Healthcare Inc.*, 2023 WL 2894939, at *12 (D. Del. Apr. 11, 2023) (Andrews, J.) (agreeing with defendant that inventor's "own testimony, as a named inventor, would seem to carry limited weight. He does not serve as a stand-in

[5] Indeed, this Court expressed skepticism that Mr. Mita's decision to try twice-daily dosing was based on a scientific approach, commenting that "it sounded mystical." Tr. at 545:5-13.

for a POSA, or for the industry."); *Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 616–17 (D. Del. 2018) (Bryson, C.J.) ("the Court finds the inventors' testimony that they were surprised by the results of the hepatic impairment study does not provide significant support for Pernix's position on non-obviousness.").

(3) The Benefits of LONSURF® Are Not Commensurate in Scope to Claim 13

Defendants also maintain that claim 13 is not commensurate in scope with the LONSURF® label. Claim 13 plainly does not reference a 28-day schedule, or a two-week rest period following two weeks of administering the drug on a five-days on, two-days off schedule. Defs.' Br. at 36-37. Plaintiffs' fixation on the absence of the words "16-day rest period" from the label is misleading, as the label indeed requires a 16-day rest period (i.e., days 13-28 of each 28-day cycle) during which the patient does not take the drug. Defendants respectfully believe this issue was adequately addressed in its Opening Brief, at pp. 36-37, and need not be repeated here.

(4) There Is No Evidence of Industry Praise for Claim 13

Defendants respectfully believe this issue also was adequately addressed in its Opening Brief, at p. 47, and need not be repeated here. However, Defendants note that Plaintiffs' statement that "The Claimed *Dosing Regimen*

Led to Industry Praise for LONSURF®" is misleading because the articles discussed by Dr. Goldberg do not praise the dosing regimen. Pls.' Br. at 28.

(5) Commercial Success

Defendants explained in their opening brief that commercial success is not probative of non-obviousness in the highly regulated market of pharmaceutical products. The chain of inferences supporting commercial success considerations does not logically apply to the U.S. pharmaceutical market due to the statutory rights afforded to innovator companies and regulatory rules surrounding FDA approvals. *See* Defs.' Br. at 40-42; *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005).

Plaintiffs have not sufficiently addressed this issue. Instead, Plaintiffs unpersuasively attempt to distinguish this case from *Merck* and note that the Federal Circuit previously has considered commercial success in ANDA cases. *See* Pls.' Br. at 48-49. Defendants respectfully submit that the *Merck* decision is clear on its face and supports Defendants' position here.

IV. CLAIM 13 IS INVALID FOR LACK OF WRITTEN DESCRIPTION

As Plaintiffs correctly note, the factual inquiry for written description is whether the specification conveys with reasonable clarity to a hypothetical investigator that, as of the filing date, the applicant was in possession of the claimed invention. Pls.' Br. at 49 (citing 35 U.S.C. § 112). However, the

remaining advocacy in Taiho's Brief with respect to written description misses the mark.

The fundamental reason that claim 13 is invalid for lack of written description is that a POSA would not understand, based on the four corners of the specification alone, that the inventors were in possession of a method for treating *colorectal cancer* by administering TAS-102 in *two* divided portions per day. The specification generally discloses administering TAS-102 in 2 to 4 divided portions. The specification includes one example that uses twice daily dosing, but that study involved *breast cancer patients*, not colorectal cancer patients. Dr. Ratain persuasively testified that a POSA would not understand breast cancer dosing to apply to colorectal cancer. Defs.' Br. at 38-40.

Dr. Ratain's testimony regarding what the specification conveys is from the perspective of a POSA, as he meets the agreed qualifications of a POSA. Defs.' Br. at 24; Pls.' Br. at 11-12. Moreover, Defendants have never argued that the written description requirement "demand[s] either examples or an actual reduction to practice." Pls.' Br. at 50. Rather, Defendants maintain the four corners of the specification do not disclose administration of two divided portions of TAS-102 to patients with digestive or colorectal cancer. Defs.' Br. at 49. Taiho's suggestion to the contrary should be rejected.

V. CONCLUSION

Defendants have proven by clear and convincing evidence that claim 13 is invalid for obviousness and for lack of written description. Judgment should therefore be entered in Defendants' favor.

RICHARDS LAYTON & FINGER, P.A.

/s/ Kelly E. Farnan
Kelly E. Farnan (#4395)
Tyler E. Cragg (#6398)
One Rodney Square
920 N. King Street
Wilmington, DE 19801
(302) 651-7700
farnan@rlf.com
cragg@rlf.com

Dated: May 11, 2023

Of Counsel:

Christopher J. Sorenson
MERCHANT & GOULD P.C.
150 South Fifth Street, Suite 2200
Minneapolis, MN 55402
612-332-5300
csorenson@merchantgould.com

Attorneys for Defendants Natco Pharma Ltd. and Natco Pharma Inc.

MORRIS JAMES

/s/ Kenneth Laurence Dorsney
Kenneth Laurence Dorsney (#3726)
Cortlan S. Hitch (#6720)
500 Delaware Avenue
Suite 1500
Wilmington, DE 19899
(302) 888- 6855
kdorsney@morrisjames.com
chitch@morrisjames.com

Of Counsel:

William D. Hare
Christopher Casieri
MCNEELY, HARE & WAR, LLP
12 Roszel Road, Suite C104
Princeton, NJ 08540
(202) 640-1801
bill@miplaw.com
chris@miplaw.com

Attorneys for Defendants Eugia Pharma Specialities Ltd., Aurobindo Pharma Ltd., and Aurobindo Pharma U.S.A., Inc.

SMITH, KATZENSTEIN, & JENKINS LLP

/s/ Daniel A. Taylor
Neal C. Belgam (#2721)
Daniel A. Taylor (#6934)
1000 N. West Street, Suite 1501
Wilmington, DE 19801
302-652-8400
nbelgam@skjlaw.com
dtaylor@skjlaw.com

Of Counsel:

Constance Huttner
WINDELS MARX LANE & MITTENDORF, LLP
One Giralda Farms
Madison, NJ 07940
973-966-3200
chuttner@windelsmarx.com

Attorneys for Defendant Accord Healthcare Inc.

SMITH, KATZENSTEIN, & JENKINS LLP

/s/ Daniel A. Taylor
Neal C. Belgam (#2721)
Daniel A. Taylor (#6934)
1000 N. West Street, Suite 1501
Wilmington, DE 19801
302-652-8400
nbelgam@skjlaw.com
dtaylor@skjlaw.com

Of Counsel:

Constance Huttner
Louis Weinstein
Joshua Miller
WINDELS MARX LANE & MITTENDORF, LLP
One Giralda Farms
Madison, NJ 07940
973-966-3200
chuttner@windelsmarx.com
lweinstein@windelsmarx.com
jmiller@windelsmarx.com

Jason Lief
WINDELS MARX LANE & MITTENDORF, LLP
156 West 56th Street
New York, NY 10019
Madison, NJ 07940
jlief@windelsmarx.com

Attorneys for Defendants MSN Laboratories Private Ltd., and MSN Pharmaceuticals Inc.